PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2004/007297	International filing date *(day/month/year)* 05.07.2004	Priority date *(day/month/year)* 17.07.2003
International Patent Classification (IPC) or national classification and IPC G01N33/50		
Applicant UNILEVER N.V. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2004	12.08.2005
Name and mailing address of the International preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Vanhalst, K Telephone No. +31 70 340- 3075

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007297

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-11 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-9
	No:	Claims	1-4,10,11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Cited documents**

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: JI JIAFU ET AL: 'Comprehensive Analysis of the Gene Expression Profiles in Human Gastric Cancer Cell Lines' ONCOGENE, vol. 21, no. 42, 19 September 2002 (2002-09-19), pages 6549-6556, XP002261627 ISSN: 0950-9232

D2: WO 02 090387 A (CHOPIN LISA KERSTIN ;JEFFERY PENELOPE LORRELLE (AU); UNIV QUEENSLA) 14 November 2002 (2002-11-14)

D3: KARBONITS M., ET AL: 'The Expression of the Growth Hormone Secretagogue Receptor Ligand Ghrelin in Normal and Abnormal Human Pituitary and Other Neuroendocrine Tumors' J. CLIN. ENDOCRINOL. METAB., vol. 86, no. 2, 28 - 28 October 2000, pages 881-887, XP002261629

D4: RINDI GUIDO ET AL: 'Ghrelin expression in gut endocrine growths' HISTOCHEMISTRY AND CELL BIOLOGY, vol. 117, no. 6, June 2002 (2002-06), pages 521-525, XP002261691 ISSN: 0948-6143

2. **Clarity** (Art. 6 PCT)

1. The term "model" used in claims 1 and 2 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature(s) to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

3. **Novelty** (Art. 33(2) PCT)

1. Taken the above objection into account, the only technical features stated in claims 1-2 are growing a gastric adenocarcinoma cell line (e.g. RF-1 or RF-48) capable of producing ghrelin, in a suitable culture medium, since the term

"model" does not add any additional technical features.

1. D1 therefore discloses (the references in parentheses applying to this document):

2. A model suitable for the study of the (regulation of) expression, synthesis and/or secretion of ghrelin, comprising in vitro culture of a cell line derived from a gastric adenocarcinoma being capable of producing ghrelin, and said model also comprising a medium suitable for growing said cell line; the above stated model, wherein the cell line is selected from RF-1, having ATCC number CRL-1864 and RF-48, having ATCC number CRL-1863 (abstract, p 6552, column 1, line 21- column 2, line 24 and Figure 2), claims 1 and 2.

2. D1 furthermore discloses (the references in parentheses applying to this document):

1. A method suitable for assessing the (regulation of) expression, synthesis and/or secretion of ghrelin, wherein a cell line derived from a gastric adenocarcinoma and capable of producing ghrelin when grown in a suitable medium, is grown is such medium; the above stated method, wherein the cell line is selected from RF-1, having ATCC number CRL-1864 and RF-48, having ATCC number CRL-1863 (abstract, p 6552, column 1, line 21- column 2, line 24 and Figure 2), claims 3 and 4.

3. D1 furthermore discloses (the references in parentheses applying to this document):

1. The use of a cell line derived from a gastric adenocarcinoma capable of producing ghrelin in vitro when grown in a suitable medium; the above stated use, wherein the cell line is selected from RF-1, having ATCC number CRL-1864 and RF-48, having ATCC number CRL-1863 (abstract, p 6552, column 1, line 21- column 2, line 24 and Figure 2), claims 10 and 11.

4. The subject-matter of claims 1-4 and 10-11 is therefore not new and the application does not fulfill the requirements of Article 33(2) PCT.

4. **Inventive step** (Art. 33(3) PCT)

1. D1 which is considered to represent the most relevant state of the art regarding the subject-matter of claims 5 and 6, discloses (cf. abstract, p 6552, column 1, line 21- column 2, line 24 and Figure 2) a method, suitable for assessing the (regulation of) expression, synthesis and/or secretion of ghrelin, from which the subject-matter of claims 5 and 6 differs in that the specific growth conditions (growth medium, temperature, atmospheric condition, changing of medium) of the used cell lines are explicitly mentioned. These features are however implicit to the use of the cell lines and are clearly stated on the website of the supplier (cf. www.atcc.org). The subject-matter of claims 5 and 6 can therefore not be seen as comprising an inventive step.

2. D3 which is considered to represent the most relevant state of the art regarding the subject-matter of claims 7 and 8, discloses (cf. abstract and materials and methods, p 881-884) a method, suitable for assessing the (regulation of) expression, synthesis and/or secretion of ghrelin, from which the subject-matter of claims 7 and 8 differs in that a gastric adenocarcinoma cell line is used in stead of another endocrine tumour cell line. The use of such a cell line does not result in an unexpected technical effect.

    1. The problem to be solved by the present invention may therefore be regarded as the provision of an alternative ghrelin-producing cell line for the assessment of ghrelin expression and/or secretion. The solution would then be using a gastric adenocarcinoma cell line.

    2. It would however be obvious to the person skilled in the art to use a cell line of gastric endocrine origin, since it is clearly known from the literature (D4, cited by the applicant) that ghrelin expression is highest in cells of gastric origin. Therefore, the person skilled in the art would easily come to using the RF-1 or RF-48 cell line in the method according to D3, since these cells are known to be of gastric endocrine origin. The subject-matter of claims 7 and 8 does therefore not comprise an inventive step.

3. D2 which is considered to represent the most relevant state of the art regarding the subject-matter of claim 9, discloses (cf. abstract, p 3, line 5 - 28 and claims 22 and 23) a method, suitable for assessing the (regulation of) expression, synthesis and/or secretion of ghrelin, from which the subject-matter of claim 9 differs in that a gastric adenocarcinoma cell line is used in stead of another tumour cell line. The use of such a cell line does not result in an unexpected technical effect.

   1. The problem to be solved by the present invention may therefore be regarded as how to provide an alternative ghrelin-producing cell line for the assessment of ghrelin expression and/or secretion. The solution being the use of a gastric adenocarcinoma cell line.

   2. It would however be obvious to the person skilled in the art to use a cell line of gastric endocrine origin, since it is clearly known from the literature (Document D4, cited by the applicant) that ghrelin expression is highest in cells of gastric origin. Therefore, the person skilled in the art would easily come to the solution of using the RF-1 or RF-48 cell line in the method according to D3, since these cells are known to be of gastric endocrine origin. The subject-matter of claim 9 does therefore not comprise an inventive step.

4. In conclusion, the subject-matter of claims 5-9 is not inventive and the application does subsequently not fulfill the requirements of Article 33(3) PCT.

5. **Industrial applicability** (Art. 33(4) PCT)

   1. The subject-matter of claims 1-11 fulfills the requirements of Industrial applicability, as laid down in Article 33(4) PCT.